Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (currently amended) A method of separating a first ligand from a second ligand in an affinity matrix system, wherein the first ligand associates *in vivo* with the second ligand and wherein the first ligand and the second ligand associate with each other by electrostatic forces, comprising the steps:

(a) Obtaining a sample containing biological complexes that include the first ligand and the second ligand;

(b) Non-covalently i~~I~~mmobilizing the second ligand on an affinity matrix;

(c) Removing unbound substances from the affinity matrix;

(d) Separating the first ligand from the immobilized second ligand, which remains bound to the affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the second ligand; and

(e) Optionally, analyzing the separated first ligand.

2. (original) A method of separating a first ligand from a second ligand in an affinity matrix system, wherein the first ligand associates *in vivo* with the second ligand, wherein the first ligand and the second ligand associate with each other by electrostatic forces, and wherein the second ligand is a recombinant fusion protein containing at least one affinity tag, comprising the steps:

(a) Introducing into a cell or organism a recombinant nucleic acid molecule encoding a fusion protein comprising the second ligand fused to at least one affinity tag that can selectively bind to an affinity matrix;

(b) Expressing the fusion protein;

(c) Obtaining a sample containing biological complexes that include the first ligand and the fusion protein;

(d) Immobilizing the fusion protein on the affinity matrix via the affinity tag;

(e) Removing unbound substances from the affinity matrix;

(f) Separating the first ligand from the immobilized fusion protein, which remains bound to the affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the fusion protein; and

(g) Optionally, analyzing the separated first ligand.

3. (original) A method of separating a first ligand from a second ligand in an affinity matrix system, wherein the first ligand associates *in vivo* with the second ligand, wherein the first ligand and the second ligand associate with each other by electrostatic forces, and wherein the second ligand is a recombinant fusion protein containing at least two different affinity tags, comprising the steps:

(a) Introducing into a cell or organism a recombinant nucleic acid molecule encoding a fusion protein comprising the second ligand fused to at least two different affinity tags that can selectively bind to different affinity matrixes;
(b) Expressing the fusion protein;
(c) Obtaining a sample containing biological complexes that include the first ligand and the fusion protein;
(d) Immobilizing the fusion protein on a first affinity matrix via a first affinity tag;
(e) Removing unbound substances from the first affinity matrix;
(f) Separating the fusion protein from the first affinity matrix;
(g) Immobilizing the fusion protein on a second affinity matrix via a second affinity tag, which is different than the first affinity tag;
(h) Removing unbound substances from the second affinity matrix;
(i) Separating the first ligand from the immobilized fusion protein, which remains bound to the second affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the fusion protein; and
(j) Optionally, analyzing the separated first ligand.

4. (original) A method of separating a first ligand from a second ligand in an affinity matrix system, wherein the first ligand associates *in vivo* with the second ligand, wherein the first ligand and the second ligand associate with each other by electrostatic forces, and wherein the second ligand is a protein complex containing two or more subunits of which are fused to different affinity tags, comprising the steps:

(a) Introducing into a cell or organism recombinant nucleic acids molecules encoding fusion proteins comprising the two or more subunits of which are fused to different affinity tags that can selectively bind to different affinity matrixes;
(b) Expressing the fusion proteins;

(c) Obtaining a sample containing biological complexes that include the first ligand and the fusion proteins;
(d) Immobilizing the fusion proteins on a first affinity matrix via a first affinity tag;
(e) Removing unbound substances from the first affinity matrix;
(f) Separating the fusion proteins from the first affinity matrix;
(g) Immobilizing the fusion proteins on a second affinity matrix via second affinity tag, which is different than the first affinity tag;
(h) Removing unbound substances from the second affinity matrix;
(i) Separating the first ligand from the immobilized fusion proteins, which remain bound to the second affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the fusion proteins; and
(j) Optionally, analyzing the separated first ligand.

5. (previously presented) The method according to claim 1, wherein the second ligand is immobilized selectively on the affinity matrix coated with antibody that binds to the second ligand.

6. (previously presented) The method according to claim 2, wherein the at least one affinity tag can bind selectively to the Fc domains of immunoglobulin.

7. (original) The method according to claim 6, wherein the at least one affinity tag contains one or more IgG binding regions of Staphylococcus aureus Protein A or Streptococcal protein G.

8. (original) The method according to claim 2, wherein the at least one affinity tag can be separated selectively from the affinity matrix by treatment with a chemical agent.

9. (original) The method according to claim 8, wherein the at least one affinity tag is selected from the group consisting of GST-tag, SBP-tag, calmodulin binding peptide and maltose binding peptide.

10. (previously presented) The method according to claim 3, wherein the second ligand is separated from the first affinity matrix by enzymatic cleavage.

11. (original) The method according to claim 10, wherein the enzymatic cleavage is cleavage by TEV protease.

12. (previously presented) The method according to claim 3, wherein the immobilization in step (d) is performed by binding to a solid support coated with a specific antibody and the separation in step (f) is performed by addition of the same antibody.

13. (previously presented) The method according to claim 3, wherein the immobilization in step (g) is performed by binding to a solid support coated with a specific antibody.

14. (previously presented) The method according to claim 3, wherein the first affinity tag can bind selectively to the Fc domains of immunoglobulin.

15. (original) The method according to claim 14, wherein the first tag contains one or more IgG binding regions of Staphylococcus aureus Protein A (SpA-tag) or Streptococcal protein G (SpG-tag).

16. (previously presented) The method according to claim 3, wherein the first affinity tag can be separated selectively from the first affinity matrix by treatment with a chemical agent.

17. (original) The method according to claim 16, wherein the first affinity tag is from the group consisting of GST-tag, SBP-tag, calmodulin binding peptide and maltose binding peptide.

18. (previously presented) The method according to claim 3, wherein the second affinity tag can be separated from the first affinity matrix by treatment with a chemical agent.

19. (original) The method according to claim 18, wherein, the second affinity tag is from the group consisting of GST-tag, SBP-tag, calmodulin binding peptide and maltose binding peptide.

20. (previously presented) The method according to claim 3, wherein the second affinity tag can bind selectively to the Fc domains of immunoglobulin.

21. (original) The method according to claim 20, wherein the second tag contains one or more IgG binding regions of Staphylococcus aureus Protein A (SpA-tag) or Streptococcal protein G (SpG-tag).

22. (previously presented) The method according to claim 1, wherein the first and second ligand are separated by decreasing the electrostatic forces between the first and second ligand by increasing the ionic strength of the system.

23. (original) The method according to claim 22, wherein the ionic strength of the system is increased with a chemical agent.

24. (original) The method according to claim 23, wherein the chemical agent is KCl.

25. (original) The method according to claim 23, wherein the change of the concentration of the chemical agent is less than 30 mM.

26. (previously presented) The method according to claim 23, wherein the change of the concentration of the chemical agent is between 30 mM and 2 M.

27. (cancelled)

28. (cancelled)

29. (previously presented) The method according to claim 1, wherein the first and second ligand are separated by decreasing the electrostatic forces between the first and second ligand by changing the pH of the system.

30. (previously presented) The method according to claim 1, wherein the first ligand is separated from the second ligand by enzymatic treatment that modifies the second ligand.

31. (previously presented) The method according to claim 1, wherein the first ligand is separated from the second ligand by enzymatic treatment that modifies the first ligand.

32. (previously presented) The method according to claim 1, wherein after the separation of the second ligand from the first ligand, the immobilized second ligand is mixed with a cellular lysate from a different or same organism, and after removal of the unbound substances, the first ligand is separated from the second ligand.

33. (cancelled)

34. (previously presented) The method according to claim 1, wherein a chemical or biomolecule is identified as a drug or pre-drug by its capability to separate selectively the first ligand from the second ligand and/or affect selectively the separation of the first ligand from the second ligand when it is added to or removed from the cellular lysate and/or the affinity matrix system; and wherein the change of the concentration of the chemical or biomolecule is below 30 mM.

35. (original) The method according to claim 34, wherein the second ligand is a protein which contains at least one mutation.

36. (original) The method according to claim 34, wherein the second ligand associates directly or indirectly with a protein that contains at least one mutation.

37. (previously presented) The method according to claim 34, wherein the chemical or biomolecule is designed, synthesized and/or selected for testing by the capability of the chemical or biomolecule to bind to the first ligand or second ligand.

38. (previously presented) The method according to claim 35, wherein the chemical or biomolecule is designed, synthesized and/or selected for testing by one or more of the following features: (a) capability of the chemical or biomolecule to bind selectively to the mutated protein; (b) the chemical or biomolecule contains at least one electrostatic charge that is identical to the charge that has been changed as a result of the mutation, and (c) after binding of the chemical or biomolecule to the mutated protein, the electrostatic charge is located at distance between 0 and 0.5 nanometers from the mutated amino acid in the mutated protein.

39. (previously presented) The method according to claim 1, wherein the second ligand is an enzyme.

40. (previously presented) The method according to claim 1, wherein the second ligand is a substrate for an enzyme.

41. (previously presented) The method according to claim 1, wherein the second ligand is an enzyme and a substrate for a different enzyme.

42. (original) The method according to claim 41, wherein the second ligand is RNA polymerase or DNA polymerase.

43. (withdrawn) A method for identifying protein-protein association as a putative cause for a disease, comprising associating the disease with a mutation that changes the electrostatic properties of a protein by replacing Lysine and/or Arginine and/or Aspartate and/or Glutamate and/or Histidine with an uncharged or oppositely charged amino acid.

44. (withdrawn) A method for identifying protein-protein association as a putative cause for a disease, comprising associating the disease with a mutation that changes the electrostatic properties of a protein by replacing an amino acid with Lysine and/or Arginine and/or Aspartate and/or Glutamate and/or Histidine.

45. (previously presented) The method according to claim 1, wherein ligand-ligand association as a putative cause for a disease is identified.

46. (previously presented) The method of claim 45, wherein the disease comprises Norrie disease, Alzheimer's disease, Parkinson's disease, beta3-adrenergic receptor gene mutation, achondroplasia, sickle cell anemia, thrombosis, epilepsy, Usher syndrome, Creutzfeldt-Jakob disease, pancreatic adenocarcinoma, Alexander's disease, aortic aneurysm, Tay-Sachs disease, xeroderma pigmentosum, systemic mast cell disease, neonatal type 2 Gaucher disease, multiple epiphyseal dysplasia, Ehlers-Danlos syndrome, or alpha 1-antitrypsin deficiency.

47. (previously presented) The method according to claim 1, wherein the second ligand is a glycoprotein and the affinity matrix is lectin coated beads.

48. (previously presented) The method according to claim 1, wherein the second ligand is a nucleic acid, which is part of a nucleoprotein complex and the affinity matrix, consists of immobilized nucleic acid with complementary sequence.

49. (previously presented) The method according to claim 1, wherein the second ligand is a nucleic acid, which is part of a nucleoprotein complex and is genetically engineered so that it contains a poly-Guanosine and the affinity matrix consists of immobilized poly-dCytosine.

50. (withdrawn) A reagent kit comprising a buffer for preparation of cellular lysate and washing buffer and wherein the buffers are capable of maintaining the electrostatic forces between the first ligand and the second ligand.

51. (withdrawn) The reagent kit according to claim 50 wherein the ionic strength of the buffers is between 0 and 400 mM.

52. (withdrawn) The reagent kit according to claim 50 additionally comprising at least one chemical agent for separating the first ligand from the second ligand and wherein the chemical agent is capable of decreasing the electrostatic forces between the first ligand and the second ligand.